2013 Presidential Address: Just Another President's Speech (but It's All about You)[1]

Jeffrey C. Murray[2,*]

First, I thank Mary-Claire for the wonderful introduction. As Mary-Claire noted, I moved here in 1967, when the Red Sox clinched the pennant for the first time after a long drought and then went on to play the St. Louis Cardinals, as they do again this year. I became a Red Sox fan in 1967 and survived the disappointments of 1975 and 1986, but eventually in 2004 they did win, and so I'm excited to now have the opportunity to be in Boston once again for a World Series.

I also wanted to acknowledge that we are celebrating the 50th anniversary of Massachusetts's becoming the first state to mandate phenylketonuria screening for newborns. This is one of the first and possibly the most impactful public-health successes that genetics has brought to us, and this milestone will resonate in talks we hear over the next few days as we increasingly see the application of genetic knowledge to directly benefit individuals.

Today, I am going to focus in part on something that most of you might not feel is an exciting topic—a strategic plan for The American Society of Human Genetics (ASHG). But, first I will summarize a bit of the history of the Society—a few of the events that have helped form my career—and then will spend a bit of time talking about an ASHG strategic plan to stimulate you over the course of the rest of this meeting to think about the Society. We are at a critical time in genetics, and we hope that meetings like this can help to stimulate us to think about where we might be a few years from now. I also wanted to recognize our staff, particularly Pauline Minhinnett and Joe McInerney, our new executive vice president (EVP), who have brought this meeting together, who had to deal with changes in our EVP position, and who were acutely challenged in having to deal with the governmental budget crisis that took place over the last couple of months. Finally, I also thank all of you general members, committee members, and board members who make the Society what it is. My somewhat tongue-in-cheek comment is in part an acknowledgment of the fact that although these speeches recur year after year, it is the members who provide for societal stability. Most of you are unlikely to remember anything about this talk, but I do hope that you will remember your mission as a member of the Society and that you work to improve ASHG, your own work, and the lives of others.

In a terrific article reviewing these meetings, Terry Hassold and Bronya Keats[1] showed a curve of attendance over the last 60 years. Their graph demonstrates an enormous burst of growth that began in the 1970s, when we had only a few hundred attendees at the annual meeting, up to the 6,000 or 7,000 individuals who attend these meetings today. So the good news is that we grew very rapidly and became a large society that offers many, many benefits to our membership. A possible concern is also illustrated in their figure, where you can see a leveling off in meeting attendance over the last decade, suggesting that we might have saturated the human genetics market—an issue we need to consider as we go forward.

I have also seen my personal history reflected in the history of human genetics and ASHG. I was born in 1949, the Society in 1948, and as we all know, the 1950s heralded both the structure of DNA and the normal chromosome count of 46. I had a brother born in 1951 with trisomy 21, although his formal diagnosis wasn't made until his

[1]This article is based on the address given by the author at the meeting of The American Society of Human Genetics (ASHG) on October 22, 2013, in Boston, MA, USA. The audio of the original address can be found at the ASHG website.

[2]Department of Pediatrics, University of Iowa, Iowa City, IA 52242, USA
*Correspondence: jeff-murray@uiowa.edu

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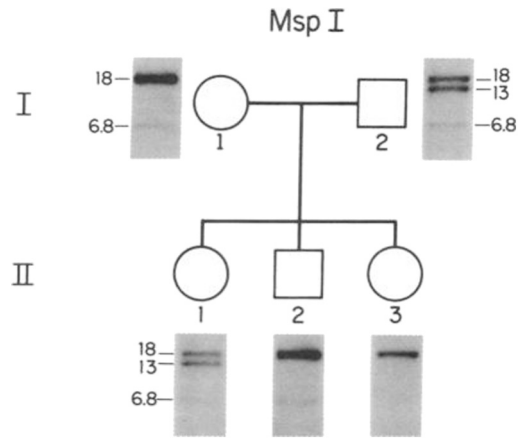

Figure 1. Pedigree of a Family Affected by the MspI Polymorphism
The 18 and 13 kb fragments are codominant alleles. The 6.8 kb fragment shown is a nonpolymorphic band detected with MspI. A 5 kb band found only in association with the 13 kb band is not shown here, and two faint bands are seen between the 13 and 6.8 kb fragments.

autopsy following his death at age 29. We suffered under the standards of care of the medical community at the time in that he was placed into an institution where he stayed until his death. He never had surgery for his correctable congenital heart disease and died as a complication of that condition. He also bore a startling physical resemblance to me, his older brother, demonstrating early on for me that children and adults with Down syndrome have many of their physical and behavioral traits embedded in their DNA, just as any other family member might. His treatment was very much in contrast to that of my niece once removed, who was also born with trisomy 21 just a few years ago and who had very successful surgery performed shortly after birth. She is fully integrated into her family with her wonderful, loving parents and younger brother, and I think she demonstrates the growth in not only our knowledge and our technology but also our ability to deliver medicine that can provide a family context to the benefit of all.

It was in the 1960s, and just before I came to college here in Boston, that while taking high school biology from my teacher, Mr. Pine, I was most likely imprinted with a career in genetics by his tangible enthusiasm for questions of genetics in general and specifically around finally knowing the exact chromosome number of 46. He was the first among many of my teachers who conveyed a love and enchantment with our discipline. Many of us will have similarly benefitted from charismatic teachers, and it is highly appropriate that a major mission of our Society lies in fostering college and precollege genetics awareness.

While attending school in Boston, I was very fortunate to get a job in a lab where DNA technology was at the forefront. I worked in Gobind Khorana's lab for several years as a lab technician on DNA synthesis for his postdoctoral fellows Marv Caruthers and Hans van de Sande; there I received my first training on how to plan and execute an experiment. A few years later, in 1975, probably the single most important stimulus to my future career came when I went to medical school at Tufts and had the opportunity to work under Murray Feingold for a summer on a research study on the effect of maternal diabetes on the fetus. Probably more important than the research (which was never published but did show an increase in neural-tube defects [NTDs]) was the chance to observe Murray and his fellow Lou Bartosheshky in their dedicated care for patients. Over the 7 years that I was a medical student and a resident at Tufts, I repeatedly saw their incredible commitment to the patients and their families. Although I will never achieve this same capacity for passion and commitment, I'll always be grateful for the message that he sent about the primary importance of patient and family care. I was equally lucky to take my first faculty position in Iowa, where the same messages were passed on to me by my mentor there, Jim Hanson.

After I left Tufts, I went to a postdoctoral fellowship under Arno Motulsky, and it was under Arno's direction that my love for molecular biology and its application in human genetics flowered. In parallel, Arno fostered my interest in the social and ethical aspects of genetics. Shown here is a figure taken from an article that was the first scientific article on which I played a major role (Figure 1). It shows a single SNP, or as it was known back in the day, a restriction-fragment-length polymorphism, segregating in Arno's family. We were able to get a very nice publication in *Proceedings of the National Academy of Sciences*[2] because we identified a few SNPs. It is likely that there are over a billion SNPs characterized every day now. The technology advances where you can go from identifying a single SNP and it's having some resonance in the scientific community to the scale on which genomics operates today is truly amazing. I'm also very grateful to Arno and his family, who provided their DNA samples for our analysis (Figure 1).

Presidential lectures call us to look back at what people before us have said, so I'm going to use some quotations from a few earlier presidents to illustrate some points about the Society and to segue into our strategic planning goals.

Jim Neel was the first president who I knew personally, and he noted, "It would be redundant in this company to extol the advantages of membership in [ASHG]…Our Society, by what I am sure is careful design, has adopted an entirely different pattern…Apparently the only requirement for our Presidential Address is that the speaker talk about some subject close to his heart at the moment."[3] Clarke Fraser, who I think was probably the coolest president, said this: "It was suggested that I should call my talk 'Ponderings of a Peripatetic Pediatrician,' but the fact that I'm not a pediatrician spoils the alliteration. So I will air some thoughts that are either too trivial, or vague, or so completely unsupported by data, that I could not present them anywhere but in a Presidential address."[4] So, I'm going to take advantage of Professor Fraser's encomium and do some speculating.

Clarke Fraser was the first president (in 1961) who mentioned DNA in his address. I was surprised that it took eight years after the DNA structure was identified for DNA to get a mention in a presidential address. Fraser was prescient also in that he said, "Let's admit that the DNA-RNA code isn't the whole answer. There are, no doubt, other systems that transmit genetic information…* that may be very important in developmental processes. It may well be that not all familial, intrinsically determined diseases and defects will be traced to alterations in the DNA."[4] Now, some 50 years later, this insight mirrors many of the ways in which we now think about the genetic causes of disease residing not only in the DNA sequence.

Victor McKusick, who is probably our president most embedded in all aspects of genetics, talked at length about the clinical connections that we have in our Society. In 1974 he noted, "Do we wish to become involved with credentialing, recertification, formal continuing education, self-assessment, quality assurance, medical audit?…Questions about credentialing of non-MD's who play important roles in the delivery of genetic services will arise. Jurisdictional disputes between medical genetics and laboratory medicine…over cytogenetic and biochemical determination conceivably will also arise. Questions of reimbursement for genetic services by third-party payers have already arisen."[5] As Victor predicted, we soon went on to confront many of these issues (and we deal with them still) during our separation from the American College of Medical Genetics and our split from the genetic counselors. As Victor noted, "When some form of national health insurance is implemented, these questions will become even more pressing."[5] Well, it's hard to think of anything that's been more pressing for all of us over the last few months than the disputes that have arisen over the Affordable Care Act and the devastating impact that it has had on everybody in this audience in terms of not only their research but also their ability to provide care and pursue their careers.

I was fortunate to be working in Arno's lab when he went to Israel in the early 1980s to participate in a trial in absentia of Josef Mengele, who had been a physician in Auschwitz and who tortured and experimented on twins and many others. In his address, Arno said, "Let us not forget that human genetics was horribly misused by the Nazi government of Germany in the 1930s. Somewhat later, from the opposite end of the political spectrum, the Lysenkoists destroyed human genetics in the Soviet Union. As responsible human geneticists, we must speak out and differentiate those findings which are generally accepted biological realities from others which are interpretations and flights of fancy."[6] One of the most valuable lessons that came out of my contact with Arno was the recognition of how important politics is in science. We continue to be challenged by the social and ethical aspects of science and medicine driven by both technology and culture.

The last comment I have on past presidents reflects on our logo outlining ASHG's mission, "To discover, to educate, and to advocate." Each of the last several presidents reached out to us as individuals to go beyond the research that we do and to do more than what we find ourselves delivering in our "day jobs." Ed McCabe had a wonderful riff on evolution and the extensive discussion of complex traits, and the selection of single-nucleotide variants via evolutionary selection reinforces that physicians should incorporate evolution and its impact as a context in which to understand disease.[7] Rod McInnes gave a very moving talk on the relationship that geneticists have with culture and talked about native Canadians and how we need to be sensitive to cultures outside our own.[8] Lynn Jorde encouraged us to extend ourselves beyond the laboratory to work to educate everyone from K–12 to judges and lawyers.[9] Finally, in her wonderful presentation last year on the scientist as a citizen of the world, Mary-Claire King helped us to see the work we do in its full global context.[10]

Let me provide a few specifics about our ASHG strategic plan. Professional societies such as ours can benefit from periodically focusing on the landscape of their field and reconsidering past mission statements in determining how to best serve their membership. An outline of a strategic vision was put together by Joe McInerney and our staff over the last several months. Three target areas rose to prominence. The first is to assess the status and likely future of research, translational medicine, education, and advocacy. The second is to ensure that we serve our membership and continue to be the leading professional society in human genetics all while working in concert with other genetic societies. Finally, the third is to consider goals and strategies for the structure and function of our Society in all of its aspects over the next 3–5 years and to begin to think beyond 5 years as well. We will have an open forum to begin this process on Thursday night and will then use websites and social media to provide additional mechanisms for input. We are particularly eager for younger members of the Society to help us think about how we can make this meeting better for all of us going forward.

Next, we have had an enormously successful journal built on a series of terrific editors who have raised the quality and impact factor of the premier journal dedicated to human genetics. All of us strive to get our best work published in the *American Journal of Human Genetics*, but the nature of journals is changing. David Nelson, our current editor, is faced with the enormous challenge of open-access journals, the generation of new journals in the same space of genetics, and the need to distinguish between print publications and electronic publications. Our Society has always had some balance between basic translational and clinical sciences, and going forward, we need to continue to consider where the fulcrum points lie. A further challenge is the balance of the subdisciplines—computational biology and bioinformatics—playing larger roles in our meetings and journal. Over our 60-year history, we have seen the waxing and waning of many different subdisciplines—clinical, biochemical, population, behavioral,

and counseling genetics, etc. Going forward, we need to be able to anticipate changes to fields and emphasis and to be leaders in working with them as they develop. Genetics continues to be controversial in that not everybody embraces genetics as something useful and important. Arguments continue to rage over genetically modified organisms, prenatal diagnosis, DNA sequencing, forensic testing, patenting, and all of the many important social, ethical, and legal challenges we confront daily.

In putting this meeting together, we were challenged by the possibility that many of our members, particularly those who are United States federal employees, might not be able to attend the meeting. Because of the government shutdown of 2013, we were forced to cancel sessions, reschedule others, and then re-reschedule still more. This sad episode of failed governance only further highlights the impact of the sequester on funding, which has dropped National Institutes of Health budgets by almost 6% over the last year, a tragic loss for science and medicine. There is no better career to be involved in than genetics and to both see the beauty of discovery and use that new knowledge to improve the health of others. But at the same time, there are the realities of how politics drives and influences funding. We must encourage our students as they become accomplished scientists and develop a passion for research to also become involved in understanding the role of politics in science and to work toward supporting those individuals who will foster those programs and research efforts that they think are most important.

A final bit of proselytizing that I will use this bully pulpit for was stimulated by an email I received from Godfrey Oakley a few weeks ago. Godfrey was at the Centers for Disease Control for many years and was the primary force behind the introduction of folic acid food fortification in the United States, which has had such an enormous impact on decreasing the burden of NTDs. Godfrey wrote to me and said, "If you haven't finished your talk yet, you might think about this," and he included a copy of an article that he and Bob Brent had written a few years ago, the topic of which was The Fierce Urgency of Now.[11] So the final message that I want to leave with you is on that urgency of now. I began doing work in the Philippines in the mid-1980s and for the first time saw children with neonatal tetanus. Over the first several years that I went to the Philippines, I would routinely see five or six infants die with neonatal tetanus in public-health hospitals serving the indigent population in the Philippines; these infants were affected because their mothers had not received tetanus vaccinations, their umbilical cords had been cut nonsterilely, and they came to care too late for treatment. I remember thinking that the first time I saw a child with tetanus, I didn't even know that tetanus was a problem that existed in the world anymore, but I soon learned that although it had been eradicated in the United States, it was still epidemic elsewhere. I had even personally benefitted from the work that the March of Dimes and others did on developing a polio vaccine. I had polio when I was 4 years old, but my own children were free from it because they were vaccinated for polio and immunized against tetanus. So when I learned that 800,000 infants were dying of neonatal tetanus each year in the mid-1980s, I was just completely astounded, particularly because not a single one of those deaths was in the United States. Over the past 30 years, through philanthropies and the World Health Organization and others, the burden of neonatal tetanus has now dropped to below 50,000, but there are still almost 50,000 unnecessary deaths a year from one totally preventable cause. The message that Godfrey and Bob had and that I am now happy to convey is that all of us need to think not only about our own science, about the patient that might be in front of us right now, and about the work that we do as a part of our own culture and education but also about spending a small part of our lives thinking about those problems that are immediately addressable right now but where we lack the political will or funding. There are babies dying today unnecessarily, and I encourage everyone here to spend at least a few percent of their lives and careers thinking about and addressing those acute problems.

Okay, the big finish. Two years ago, when I learned that I was going to be president, I received an email from Rod McInnes, who was at that time the serving president. Rod wrote to me, "Jeff, once a week for the next 2 years you will wake up at night in a cold sweat, anxious about the Presidential Address. Trust me. Ciao." Well, Rod was right, and although I can't say that every single week over those 2 years I woke up in a cold sweat some night, I can tell you that every night for the last week I have woken up in a cold sweat, so I'm very glad that this is almost over and equally glad that I had an opportunity to convey to you both a personal message and a larger message for this Society. I hope you will spend some of your time thinking about ASHG and how we can improve and also how we can address right now those issues of immediate health impact in the world at large.

Lastly, some acknowledgments. Over the years, I have had many students, staff, nurses, genetic counselors, and colleagues who have really made my scientific career enjoyable, wonderful, fun, and all the things that should encourage you who are young to go into science. I will choose four specific names to note because these are people without whom I would not have had a scientific career, nor four friends who have really made this career so enjoyable. Ken Buetow, Kaare Christensen, Brian Schutte, and Mary Marazita have all been awesome scientific colleagues who became friends and have made the life of a scientist enjoyable almost every single minute. I want to thank the staff and the membership of ASHG for the opportunity to work with all of you. Next, patients and families who I still have the opportunity to serve and who I learn from every day about their strength and their ability to carry on. And then lastly and most importantly, my wife, Ann Marie McCarthy, our oldest son, Ryan, who was born down the street at the Boston Hospital for Women Lying-In Division some 33 years ago, and our two younger

kids, Chris and Katie, my daughters-in-law, Sharmala and Alma, and our first grandchild, Fatima, all of whom will live in and make a better world.

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